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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/501,407	03/25/2005	Victor Willem Van Beusechem	253-9	9615

24336 7590 07/31/2006

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EXAMINER	
LONG, SCOTT	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 07/31/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/501,407	VAN BEUSECHEM ET AL.	
	Examiner	Art Unit	
	Scott D. Long	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *10 and 15-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9, 11-14, and 24-25* is/are rejected.

7)☒ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 July 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/11/04 & 7/14/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The examiner of record has changed. Please direct all further correspondence to Scott Long whose phone number is 571-272-9048.

Election/Restrictions

Applicant's election with traverse of group I, claims 1-14 in the reply filed on 13 February 2006 is acknowledged. The election of species, p53, with traverse, was received 5 May 2006 is acknowledged by examiner.

The traversal is on the ground(s) that the prior art used as a basis for lack of unity is not appropriate to the instant application because the adenovirus disclosed in the prior art is replication deficient/defective, whereas the adenovirus of the instant application is a replication competent recombinant adenovirus. The current examiner agrees with the applicant that the different replication status of the two adenoviruses is significant. However, the current examiner has found art that reads on claims 1-14, and does not read on most of the claims of groups II-III. For this reason, the groupings established in the initial lack of unity will be maintained.

The requirement is still deemed proper and is therefore made FINAL.

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance

with the provisions of MPEP § 821.04. Process claims that depend from or otherwise include all the limitations of the patentable product will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.**
Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Please note that after a final requirement for restriction, the Applicants, in addition to making any response due on the remainder of the action, may petition the Commissioner to review the requirement. Petition may be deferred until after final action on or allowance of claims to the invention elected, but must be filed not later than appeal. A petition will not be considered if reconsideration of the requirement was not requested. (See § 1.181.).

Claim Status

Claims 1-25 are pending. However, claims 17, and 19-23 are withdrawn from further consideration by the Examiner, pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. Claim 18 is cancelled. Claims 10 and 15-16 are withdrawn by applicant. Claims 1-9, 11-14, and 24-25 are under current examination.

Sequence Compliance

Sequence Listing and CRF have been received and are acknowledged by examiner. A statement that the Computer Readable Form (CRF) and the Sequence Listing are identical has been submitted and is acknowledged by examiner.

Oath/Declaration

The new oath or declaration, having the signatures of all inventors, received on 25 March 2005 is in compliance with 37 CFR 1.63.

Information Disclosure Statement

The Information Disclosure Statements (IDS) filed on 11 July 2004 and 14 July 2005 consisting of 3 sheets are in compliance with 37 CFR 1.97. Accordingly, examiner has considered the Information Disclosure Statements.

Priority

This application claims benefit from foreign Application No. EP/02075108.7, filed 14 January 2002 and PCT Application No. PCT/EP03/00340, filed 14 January 2003.

The instant application has been granted the benefit date, 14 January 2002, from the application EP/02075108.7.

Specification

The specification is objected to because: There is no SEQ ID NO recited on page 42, line 15, when referring to the amino acid sequence.

The specification contains sequence disclosures (page 42, line 15) that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.82(a)(1) and (a)(2) but are not present in the Sequence Listing and/or identified in the specification by sequence identifier numbers. Applicant must provide sequence identifiers, in the case that these sequence identifier numbers. Applicant must provide sequence identifiers, in the case that these sequences are not included in the original sequence submission, a paper copy and a computer readable copy of the

sequence Listing and a statement that the content of the paper and computer readable copies are the same and were applicable, include no new matter, as required by 37 CFR 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d). A full response to this Office Action must include complete response to the requirement for a Sequence Listing.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 25 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The recitation of the deleted amino acids 122-129 (LTCHEAGF) SEQ ID NO:5 is different from that taught by Fueyo et al. The Fueyo et al reference teaches that the deletion corresponds to "amino acid residues L, T, C, H, E, A, C, and F of the E1A" (Fueyo et al., page 8). Clarification is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5, 6, and 8 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to

which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in *Wands* states: "Enablement is not precluded by the necessity for some 'experimentation.'" Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a prima facie case is discussed below.

In the instant case, claim 5, 6, and 8 are not enabled for p53 dependent apoptosis based on activity of E1B-55kDa protein, E1B-19kDa protein, and E4orf6 protein.

The state of the art indicates that p53 dependent apoptosis is prevented through the action of the E1b proteins. "E1B 19K and 55K proteins provide separate mechanisms that disable the cell suicide pathway of p53" (Debbas and White, abstract).

According to Blaho et al, "the E1b 19kDa protein functionally substitutes for the activity of Bcl-2 while the E1b 55 kDa binds p53 and inhibits its function." Blaho et al. further indicate that "cells which contain viral anti-apoptotic activities, such as those conferred by the adenovirus E1b region, are resistant to [virally] induced cell death" (US-2002/0187126A1; page 14, paragraph 0113). Several studies have shown that E4orf6 and E1b-55kDa proteins function together to reduce the half-life of p53 and induce efficient p53 degradation (Querido et al., Genes Dev. 2001. 15: p. 3105)

Therefore, in view of the state of the art, one skilled in the art could not practice the invention without undue experimentation as it is broadly claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 9, 24, and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by Fueyo et al (Oncogene. 2000. 19:2-12) and as evidenced by Nevins (Human Molecular Genetics. 2001. 10(7):699-703).

Claims 1 is directed to "a replication competent recombinant adenovirus...lytic capacity...conditionally replicating...restoring factor...restoring the p53 apoptosis pathway." Fueyo et al. teach a "replication competent" recombinant virus (p.2, *Results*,

paragraph 1). Further, Fueyo et al. teach that the virus can "replicate in and lyse cancer cells" (abstract). Their virus "induced cell death even in mutant-p53 cells" (p. 7, *Treatment with Δ24*). This indicates that the Fueyo virus is capable of restoring p53 apoptosis in the target cells. Additionally, the Fueyo adenovirus replicates conditionally, "this mutant virus would be selective for tumors...most normal...cells halts...the replication of the mutant adenovirus...this adenovirus would also be able to replicate in cancer cells...but not the surrounding differentiated cells" (p.2, *Introduction*). Regarding the limitations that the coding sequence restore the p53 apoptosis pathway, Fueyo et al indicate that their adenovirus can "express a mutant E1A protein" (p.3). The "link between the Rb/E2F pathway and the p53 response" is taught by Nevin (p.700). Consequently, the p53 apoptosis pathway is restored by expression of the mutant E1A protein.

Claims 2 and 24 are directed to "human adenovirus" of "serotype 5". Fueyo et al. teach "the replication-competent Δ24 virus is a human adenovirus 5" (p. 2).

Claims 9 and 25 are directed to "a mutation in a E1A region...of the pRb-binding CR2 domain of E1A" which "comprises a deletion...amino acids 122-129 (LTCHEAGF)...of E1A." Fueyo et al, "constructed a tumor-selective adenovirus, Δ24, that carries a 24-bp deletion in the *E1A* region responsible for binding Rb protein." (abstract). The deletion corresponds to "amino acid residues L, T, C, H, E, A, C, and F of the E1A" (Fueyo et al., page 8).

Accordingly, Fueyo et al. anticipated the instant claims.

Claims 1-7, 14, and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by Chang et al. (USPat 6,638,762) as evidenced by Bressac et al. (PNAS. 1990. 87:1973-1977) and further evidenced by Moore et al. (PNAS. 1996. p.11295-11301)

Claim 1 is directed to "a replication competent recombinant adenovirus...lytic capacity...conditionally replicating...restoring factor...restoring the p53 apoptosis pathway." Chang et al. teach the limitations of claim 1, including a "cell-specific...recombinant...adenovirus" (abstract) which is "replication competent" (column 32, line 21), "replication-conditional" (abstract) and can "provide a therapeutic benefit in a tissue...from one or more heterologous gene products expressed from the vector" (abstract). Chang et al. also teach that the adenovirus has lytic capacity in target cells, "cytopathic viral lysate...the vector replicates in the infected cells as indicated by characteristic cytopathic effects and spreading of cell death" (column 30, lines 14-26).

While Chang et al does not explicitly teach that the target cells are hampered in the p53 dependent apoptosis pathway. However, Chang et al. teaches the use of their adenovirus in Hep3B cells (column 34, lines 34). Hep3B cells contain a partial-deletion of the p53 gene, resulting in no detectible p53 mRNA or protein (Bressac et al. p.1977, Table 1). This indicates that these Hep3B target cell lines are inherently hampered in the p53 dependent apoptosis pathway. Therefore this limitation of claim 1 is met.

Claims 2 and 24 are directed to "human adenovirus" of "serotype 5". Chang et al teach the limitations of claims 2 and 24, a "human adenovirus 5" (column 4, line 1).

Claim 3 is directed to "early adenovirus gene is controlled by a tumor-specific promoter." Chang et al teach the limitation of claim 3 that "a gene in the adenovirus E1 region is operably linked to the tissue-specific transcriptional regulatory control sequence. Preferably the E1a, E1b, or E2a" (column 7, lines 34-39). Chang et al. further teach the "tumor-specific promoter" (column 7, line 49).

Claim 4 is directed to a "trans-complemented adenovirus." Chang et al. teach the further limitation of claim 4 that "replication is conditioned upon the presence of a trans-acting transcriptional factor " (Col 5, lines 9-10).

Claims 5-6 are directed to the "E1B-55kDa protein" and "E1B-19kDa protein." Chang et al. teach the limitations of claims 5-6 that "the invention further embodies the use of...vectors having...essential regions...for replication...E1b19 kDa gene, or E1b 55 kDa gene" (column 17, lines 20-23).

Claim 7 is directed to "genes of the...E4 region." Chang et al. teach the limitation of claim 7, "E4 coding region" (column 17, line 18).

Claim 8 is directed to "the gene encoding...E4orf6 protein." The limitation of claim 8, E4orf6, is inherent in the E4 coding region, as described by Moore et al., "wild-type E4 genes...express the E4orf6" (p.11301).

Claim 14 is directed to "target cell is a human...cancer cells, arthritic cells, smooth muscle cells, and cells infected with a virus." Chang et al teach the limitation of claim 14 that the target cells are "tumors, ...arthritis" (column 23, lines 50-57), and "tumor types include...soft tissue...reproductive tract" (column 23, lines 47-48). Vascular smooth muscle cells are an inherent sub-type of soft tissue. The tumors of the

reproductive tract include cervical cancer which is commonly caused by human papilloma virus. Chang et al. teach activation of their tissue specific adenoviruses through "transcriptional regulatory factors include...transactivating factors produced by endogenous viral sequences such as from CMV, HIV, EBV, HSV, SV40, and other such viruses that are pathogenic...in humans" (column 9, lines 43-47). Therefore target cells infected with viruses other than the therapeutic adenovirus is taught by Chang et al.

Chang et al. teach the further limitation of claim 22 that "the methods of treatment...the tissue is abnormally proliferating, and is especially tumor tissue." (column 7, lines 11-13).

Accordingly, Chang et al. anticipate the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 and 11-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lin et al. (Cancer Research. Oct 15, 2000. 60. p.5895-5901) in view of Chang et al.

Lin at al. teach an adenovirus "p53 variant (p53 14/19) containing double substitutions at amino acid residues Leu-14 and Phe-19... p53 14/19 is deficient in mdm2 binding" (Results, p.5896). Lin et al. also teach that the adenovirus restores function in cells "which lack endogenous p53" (Transcriptional Activation, p. 5896) and "induce...apoptosis at similar levels to adenovirus *wt*-p53" (Transcriptional Activation, p.5896)

Lin et al. does not teach the replication competent adenovirus, but rather a replication defective p53 adenovirus. Lin et al. also do not teach tissue specific conditional replication.

The teachings of Chang et al. are discussed above in the 35 USC § 102 section.

Chang et al. does not teach the limitations of claims 11-13, specifically that the restoring factor is p53 and that the p53 protein lacks a functional MDM2 binding domain and a functional derivative of human p53 mutated with amino acids Leu-14 and Phe-19. These limitations are taught by Lin et al. as described above.

It would have been obvious to a person of ordinary skill in the art at the time of the invention was made to incorporate the tissue specific replication conditional control

features of Chang et al into the adenovirus p53 construct of Lin et al. which contains mutations to the MDM-2 binding site of p53.

The person of ordinary skill in the art would have been motivated to make those modifications because "p53 14/19 modified tumor suppressor gene may be a promising therapeutic agent for human cancers that express abnormally high levels of mdm2 oncogene product" (Lin et al., abstract. P.5895). Lin et al would have been motivated to incorporate the modifications of Chang et al, because the adenovirus of Lin et al. is directed to "mdm2 gene amplification in tumor types...soft tissue sarcomas, " (Introduction, p.5895). The tissue specific adenovirus of Chang et al. is suited to "tumor types include...soft tissue sarcoma" (column 23, line 47). The combined adenovirus could have enhanced anticancer effects through the addition of the improvements to the known tumor suppressor, p53, and the augmented killing effect created as the replicating virus spread its effect throughout the soft tissue sarcomas. At the time the invention was made, there would have been a reasonable likelihood of success because the state of the art involving mutagenesis and adenoviruses were commonly practiced.

Conclusion

No claims are allowed.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**. The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Dave Nguyen** can be reached on **571-272-0731**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Scott Long
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Q. JANICE LI, M.D.
PRIMARY EXAMINER